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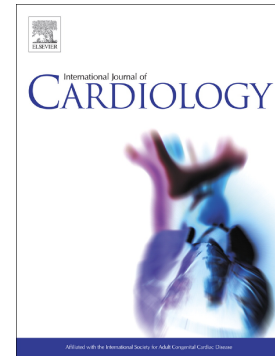
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Mortality and morbidity of major congenital heart disease related to general prenatal screening for malformations.

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### **Key words**

Congenital heart disease, fetal echocardiography, prognosis, prenatal diagnosis, prenatal malformation screening

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## Abstract

### *Background*

Major congenital heart diseases (CHD) often demand intervention in the neonatal period. Prenatal diagnosis may improve mortality by eliminating the diagnostic delay; however, there is controversy concerning its true effect.

We aimed to evaluate the effect of general prenatal screening on prognosis by comparing a period without general prenatal screening to a period with general prenatal screening.

### *Methods*

We conducted a nationwide retrospective study including live born children and terminated fetuses diagnosed with major CHD. Prenatal screening was recommended only in high risk pregnancies between 1996 and 2004, whereas general prenatal screening was recommended between 2005 and 2013. We assessed the influence of general prenatal screening on all-cause mortality, cardiac death, preoperative and postoperative 30-day mortality and complication rate.

### *Results*

1-year mortality decreased over both periods, but the decrease was greater in the screening period (Odds ratio 0.92 (CI 0.83-1.00),  $p=0.047$ ). Prenatal detection of major CHD was associated with cardiac death in the period without general screening (Hazard Ratio 2.40 (CI 1.72-3.33),  $p<0.001$ ), whereas there was no significant association once general screening was implemented. Similarly, the association between prenatal diagnosis and pre- and

postoperative mortality found in the period without general screening was insignificant after the implementation of general screening.

### *Conclusion*

Mortality in major CHD decreased throughout the study, especially in the period with general prenatal screening. However, comparing a prenatally diagnosed group with a postnatally diagnosed group is vulnerable to selection bias and proper interpretation is difficult.

**Abbreviations**

AVSD:	Atrioventricular septal defect
ccTGA:	Congenitally corrected transposition of the great arteries
CHD:	Congenital heart disease
CI:	Confidence Interval
CoA:	Coarctation of the aorta
DORV:	Double outlet right ventricle
HR:	Hazard Ratio
IAA:	Interrupted aortic arch
ICD:	International Classification of Disease
IQR:	Interquartile Range
LOS:	Length of stay
OR:	Odds Ratio
PA-IVS:	Pulmonary atresia with intact ventricular septum
PA-VSD:	Pulmonary atresia with ventricular septal defect
TGA:	Transposition of the great arteries
TOF:	Tetralogy of Fallot
TOP:	Termination of pregnancy
UVH:	Univentricular heart



## 1.1.

### Introduction

Congenital heart disease (CHD) comprises a wide variety of defects with diversity in complexity and prognosis, where major CHD typically requires intervention within the first year of life. Early diagnosis is crucial as some major CHD demand surgical or catheter-based intervention in the neonatal period. However, postnatal diagnosis is not always straightforward and may be delayed due to late presentation, misinterpretation and delayed referral.

Prenatal diagnosis eliminates the diagnostic delay, permits delivery at a tertiary centre specialised in the management of major CHD, thus enabling early invasive treatment. It is controversial whether prenatal diagnosis improves the prognosis of the child<sup>1-17</sup>. In fact, newborns with a prenatal diagnosis of a CHD have repeatedly been shown to have higher mortality than expected despite measures taken to optimise perinatal treatment<sup>1-3,7</sup>. However, a spectrum of severity exists across as well as within the individual defects, and comparing major CHD diagnosed prenatally with those diagnosed postnatally may result in selection bias<sup>5</sup>. Few studies consider this weakness when assessing the effect of prenatal screening.

Duct dependent circulation can lead to compromised oxygenation of organs, and the immaturity of certain end-organs makes infants more susceptible<sup>18</sup>. However, investigations on the effect of prenatal diagnosis on these complications are lacking.

In Denmark, the strategy for prenatal screening for congenital malformations was changed in 2004 and currently all pregnant women are offered two ultrasonic scans. By comparing a period without nationwide general prenatal screening with a period when general prenatal screening was recommended, we aimed to assess the influence of general screening

on mortality and morbidity in prenatally diagnosed children with major CHD, hypothesising that general prenatal screening improves survival and decreases postnatal complications.

## 2.1.

### Material and Methods

This nationwide study included all live born children and terminated pregnancies (TOP) with major CHD from 1996 to 2013. All Danish residents are given a unique registration number at birth, thus enabling individual identification of every person with relevant diagnoses. In January 2015, data were extracted from the Danish National Patient Registry, which is a nationwide, population-based registry carrying records of all outpatient visits and hospital admissions, and the Cause of Death Registry, which prospectively records all causes of death.

#### 2.1.1

##### *Screening procedure*

Between 1996 and 2004 the Danish Health Authority only recommended prenatal investigations in high risk pregnancies, defined by age, medical history, family history and objective findings. In 2004, the recommendations were changed and from 2005-2013 two ultrasounds were offered to all pregnant women; one to assess the nuchal fold and determine the risk of aneuploidy at 11-13 weeks, and a malformation scan at 18-20 weeks of gestation<sup>19</sup>. This examination includes cardiac evaluation: The four-chamber view has been used throughout the period and the three-vessel and outflow-tract views were fully implemented in 2010.

If at any time a CHD was suspected, the woman was referred to a tertiary centre for fetal echocardiography by a specialist in fetal medicine. If a major CHD was confirmed, the parents could apply for TOP or continue the pregnancy. If the diagnosed CHD was deemed to necessitate medical or surgical treatment shortly after birth, delivery was set to take place at a tertiary centre.

### 2.1.2

#### *Patients born with a CHD*

The National Patient Registry was used to identify patients, who at any time had been given an International Classification of Disease (ICD)-10 code corresponding to a CHD (ICD-10 code DQ20-DQ25). Extracted data included local hospital, place of birth, admission days in the first year of life, as well as all procedural and ICD-10 codes given.

Major CHD was defined as morphologically complex malformations of the heart and great arteries that usually necessitate intervention within the first year of life<sup>2,20</sup>. Included diagnoses consisted (in hierarchical order modified from Allan *et al.*<sup>21</sup>) of: 1) Univentricular heart, 2) Congenitally corrected transposition of the great arteries, 3) Truncus arteriosus, 4) Transposition of the great arteries, 5) Interrupted aortic arch, 6) Atrioventricular septal defects, 7) Double outlet right ventricle, 8) Coarctation of the aorta, 9) Ebstein's anomaly, 10) Pulmonary atresia with ventricular septal defect, 11) Pulmonary atresia with intact ventricular septum and 12) Tetralogy of Fallot.

Patient records for children with possible major CHD, based on ICD-10 code, surgical or catheter-based intervention within the first year of life or if the child had died, were examined to validate all CHD codes. Only patients with an ICD-10 code corresponding to a major CHD were included. We reviewed the records to determine if the diagnosis had

been made prenatally. If so, we evaluated the prenatal investigations and documented the findings. Only diagnoses verified postnatally or at autopsy were included.

### 2.1.3.

#### *TOP due to a CHD*

ICD-10 codes regarding TOP after 12 weeks of gestation (DO04.0-DO07.9) were used to identify possible TOPs due to a CHD in the fetus. Data (date and place of TOP, all ICD-10 codes connected to the TOP, and gestation age at TOP) were extracted from the National Patient Registry and the Registry of Abortions. We reviewed patient records and included cases where the fetus was found to have a CHD.

### 2.1.4.

#### *Definitions*

Non-cardiovascular malformation was defined as an ICD-10 code describing a congenital malformation other than a CHD (DQ00-DQ19 and DQ26-DQ89). As recommended by the European Surveillance of Congenital Anomalies<sup>22</sup>, isolated minor anomalies were excluded.

Length of stay (LOS) was defined as total number of hospital admission days in the first year of life, and morbidity was defined as the occurrence of complications, i.e. necrotizing enterocolitis, intracerebral haemorrhage, cerebral palsy, mental retardation, seizures, heart failure, liver failure or acute kidney injury.

Denmark has three tertiary centres for the management of CHD and 49 referral hospitals. Distance from a referral hospital to a tertiary centre was measured as the shortest route by vehicle.

## 2.1.5.

*Analyses*

Categorical data are presented as percentages and 95% confidence intervals (CI). Continuous data are given as median with interquartile range (IQR).  $\chi^2$ -analysis and Fisher's exact test were used to test for differences in categorical probabilities. Logistic regression analysis was applied when adjusting for confounders and assessing differences in continuous data. Splines were applied to allow analyses of the temporal changes before and after the introduction of general prenatal screening by comparing estimates before and after 2004. Estimates are given as Odds Ratio (OR).

Cox regression analysis was used when evaluating differences in survival. The non-screening period and the screening period were assessed separately and compared for temporal differences. We tested for linearity, interactions, and proportionality, using Schoenfeld residuals, and the assumptions for Cox regression analysis were met for all covariates. Survival analyses were performed individually on the major CHD diagnoses, except when event count was less than 2. Cause of death was categorised into "Cardiac death" and "Non-cardiac death", corresponding to the diagnosis on the death certificate. Cause specific cox regression was used to assess the effect of prenatal diagnosis on the hazard of cardiac death. All survival analyses were adjusted for non-cardiovascular malformation, chromosomal anomaly, sex and prematurity.

Survival analyses were performed using R-package for Windows, version 3.2.3. All other analyses were made in Statistical Analysis Software version 9.4. A p-value under 0.05 was considered statistically significant. When multiple testing was undertaken by

analysing the individual diseases separately, p-values were adjusted using Bonferroni correction, with 13 hypotheses tested.

#### 2.1.6.

##### *Declaration of Helsinki*

This study complies with the Declaration of Helsinki, and has been approved by the Danish Data Protection Agency (jr.no 2014-41-2943). The study is a registry research study, therefore, approval from the Research Ethics Committee was waived (Protocol no: H-1-2013-FSP-033).

### 3.1.

#### **Results**

2,224 live born children and 471 terminated pregnancies with major CHD were included in the study. Follow-up for live born children was median 8.5 years (IQR 2.3-13.8). Among all live born children, 15.5% were prenatally diagnosed and 93.0% (CI 90.3-95.7) of these children were delivered at tertiary centres. For children born at a referral hospital, the median distance to a tertiary centre was 65 kilometres (IQR 16-104 kilometres). Children with a prenatal diagnosis were born at a lower gestational age (270 days (IQR 264-278) vs 278 days (IQR 267-286),  $p<0.001$ ) and at a lower birth weight (3095 grams (IQR 2525-3500) vs 3330 grams (IQR 2850-3700),  $p=0.034$ ) compared with children with a postnatal diagnosis.

#### 3.1.1.

### *Mortality*

437 of the live born children (19.6%, CI 18.0-21.3) died during the first year of life at a median age of 15 days (IQR 5-86). Cardiac death was the main cause of mortality and accounted for 90.5% (CI 87.8-93.1) of deaths. This proportion changed with the introduction of general screening so that cardiac death accounted for 92.8% (CI 89.5-95.1) of deaths before the introduction and 85.6% (CI 79.5-91.7) afterwards ( $p=0.032$ ). Delivery at a tertiary centre did not alter overall survival of live born children (Hazard ratio (HR) 0.95 (CI 0.74-1.22),  $p=0.69$ ). However, long distance from referral hospital to tertiary centre increased mortality with a HR of 1.07 (CI 1.03-1.11,  $p<0.001$ ) for every 20 kilometres.

Survival curves of all-cause mortality before and after the introduction of general screening for live born children and TOP combined, as well as for live born children only, are shown in Figure 1. Correspondingly, all-cause mortality rates at 30 days and 1 year decreased throughout the study ( $p<0.001$  and  $p<0.001$  respectively). Similar results were found for cardiac death, whereas there was no development over time in non-cardiac death ( $p=0.49$ ).

Prematurity was an independent risk factor (HR 9.32 (CI 1.72-50.56),  $p=0.010$ ). Similarly, birth weight was a risk factor as a 500 g decrease in birth weight increased the mortality with a HR of 1.38 (CI 1.28-1.49,  $p<0.001$ ).

Table 1 shows TOP and 1-year mortality rates for the individual diagnoses. The highest rates were found in patients with UVH where 44.8% (CI 41.0-48.7) of all fetuses were terminated and 52.6% (CI 47.3-57.8) of live born children died within the first year of life. In general, 17.5% (CI 16.0-18.9) of fetuses with major CHD were terminated. This increased from 0.6% in 1996 to 18.4% in 2004, (OR 1.24 (CI 1.16-1.33),  $p<0.001$ ) reaching 39.1% in

2013 (OR 1.15 (CI 1.10-1.20),  $p<0.001$ ). The increase in TOP rate was not significantly affected by the introduction of general screening (OR 0.92 (CI 0.84-1.01),  $p=0.090$ ). When TOPs were included in mortality analyses for major CHD, the combined rate for TOP and 1-year mortality increased from 30.8% in 1996 to 34.2% in 2004 (OR 1.02 (CI 0.98-1.05),  $p=0.40$ ) reaching 47.8% in 2013 (OR 1.07 (CI 1.03-1.11),  $p<0.001$ ). The introduction of general screening did not significantly alter the combined 1-year mortality and TOP rate (OR 1.04 (CI 0.98-1.11),  $p=0.19$ ).

Figure 2 and Supplementary Table 1 summarise the survival for live born children according to time of diagnosis before and after the introduction of general screening. Before the introduction there was increased all-cause mortality (HR 2.52 (CI 1.84-3.44),  $p<0.001$ ) and cardiac death (HR 2.40 (CI 1.72-3.33),  $p<0.001$ ) in children, whose major CHD had been diagnosed prenatally. Similarly, in the period with general prenatal screening, there was an association between prenatal diagnosis and all-cause mortality (HR 1.94 (CI 1.37-2.74),  $p=0.003$ ). The same association was found in cardiac death, however, when we adjusted for multiple testing, this association was no longer significant (HR 1.66 (CI 1.13-1.44),  $p=0.12$ ). No significant association between prenatal diagnosis and all-cause mortality or cardiac death was found when analysing the individual CHDs (Supplementary Table 1). Excluding children with associated anomalies did not change the results significantly.

Among live born children with major CHD, 74.9% (CI 73.1-76.7) underwent surgery within the first year of life, and 9.8% died before surgery was possible. Preoperative mortality decreased from 14.8% in 1996 to 7.2% in 2004 (OR 0.94 (CI 0.88-0.99),  $p=0.020$ ) and from 8.8% in 2005 to 4.3% in 2013 (OR 0.86 (CI 0.78-0.93),  $p<0.001$ ), and was not affected by the implementation of general screening ( $p=0.19$ ). Post-operative mortality did not change significantly in the non-screening period (17.5% in 1996 to 10.6% in 2004 (OR



0.95 (CI 0.88-1.01),  $p=0.095$ ) or the screening period (4.8% in 2005 to 9.1% in 2013 (OR 0.94 (CI 0.85-1.03),  $p=0.15$ )). There was no effect of general prenatal screening on post-operative mortality (OR 0.98 (CI 0.86-1.11),  $p=0.72$ ). Prenatal diagnosis of a major CHD was associated with higher risk of preoperative (27.8% (CI 18.3-37.2) vs 10.6% (CI 8.9-12.3),  $p<0.001$ ) and postoperative 30-day mortality (24.2% (CI 13.2-35.2) vs 11.7% (CI 9.6-13.8),  $p=0.008$ ) before general prenatal screening was introduced, but not afterwards (preoperative mortality 9.1% (CI 5.5-12.6) vs 5.4% (CI 3.7-7.1),  $p=0.063$ , postoperative mortality 8.1% (CI 4.4-11.8) vs 5.4% (3.5-7.4),  $p=0.15$ ).

Non-cardiovascular malformations and chromosomal anomalies were found in 25.5% (CI 23.9-27.2) and 15.9% (CI 14.5-17.3) of live born children, respectively. The presence of a non-cardiovascular malformation was associated with increased prenatal detection (34.3% vs 28.9%,  $p=0.0072$ ), whereas no difference was found in cases with a chromosomal anomaly ( $p=0.46$ ). There were no differences in TOP rates, neither for chromosomal anomalies ( $p=0.081$ ) or non-cardiovascular malformations ( $p=0.26$ ). All-cause mortality did not differ in children with chromosomal anomalies ( $p=0.57$ ) or non-cardiovascular malformations ( $p=0.90$ ). This was also true for cardiac death ( $p=0.14$  and  $p=0.20$ , respectively).

### 3.1.2.

#### *Morbidity*

LOS in the first year of life did not differ with route of diagnosis before the introduction of general prenatal screening (37 days vs 37 days,  $p=0.17$ ). With general prenatal screening LOS was significantly longer in prenatally diagnosed children (45 days vs 38 days,

$p < 0.001$ ). Complications were found in 21.8% (CI 20.0-23.5) of live born children and the frequency increased in the period without general screening (14.2% in 1996 to 22.6% in 2004, OR 1.08 (CI 1.03-1.13),  $p = 0.001$ ) and decreased insignificantly in the period with general screening (35.3% in 2005 to 28.6% in 2013, OR 0.96 (CI 0.92-1.01),  $p = 0.086$ ). The effect of general screening was significant (OR 0.91 (CI 0.84-0.98),  $p = 0.010$ ). There was no significant difference between the pre- and postnatally diagnosed children in the occurrence of complications before (14.4% vs 17.6%,  $p = 0.52$ ) and after (32.7% vs 26.1%,  $p = 0.12$ ) the introduction of general screening ( $p = 0.12$ ).

#### 4.1.

#### Discussion

In this nationwide study on the outcome of major CHD, we evaluated the effect of general prenatal screening on mortality and morbidity. To the best of our knowledge, this is the largest nationwide, population-based study and the only to compare the outcome in a screening group with a non-screening group within the same country. We found that mortality among live born children with a major CHD has been decreasing over the past two decades, especially after the introduction of general prenatal screening. While a prenatal diagnosis was associated with higher cardiac death as well as pre- and postoperative mortality in the period without general screening, this association was not significant when general prenatal screening was introduced. There was no difference in the risk of complications; however, with general screening the prenatal group had significantly longer LOS.

##### 4.1.1.

##### *Decreased mortality*

Several steps have been taken to improve detection over the past decades; ultrasonic machinery and technique have been enhanced and sonographers have undergone extensive educational programs. Furthermore, the management of fetuses and children with CHD has been centralised and the treatment, including repair techniques, of CHD has been improved. As a result, mortality has been reduced substantially<sup>23</sup>. In our study, this was true for overall mortality as well as preoperative mortality rates. The reduced mortality may partly be due to increased prenatal detection leading to the termination of fetuses with the worst prognosis. Correspondingly, when TOP and 1-year mortality rate was considered as a whole, the rate increased throughout the study, leading to a decrease in the number of children with major CHD reaching their first birthday. Furthermore, there was a significantly stronger decrease in mortality after the introduction of general screening.

#### 4.1.2.

##### *Prenatal diagnosis and mortality*

The association between prenatal diagnosis and poor prognosis has been reported numerous times<sup>1-3,7</sup>, not only in CHD but also with other congenital malformations<sup>24,25</sup>. Most recently Wright *et al.* conducted a study of children with major CHD from a single centre. They found an adjusted HR for mortality of 1.5 associated with prenatal diagnosis<sup>7</sup>. A population-based study found a HR for mortality of 2.51 associated with a prenatal diagnosis in isolated critical CHD, which is comparable to our results<sup>2</sup>.

This association may be caused by the spectrum of severity with prenatally diagnosed major CHD having an a priori more sinister prognosis<sup>3</sup>. The four-chamber view tends to mainly detect lesions with poor prognosis<sup>26</sup>; however, with the introduction of general screening and the implementation of additional views, milder cases of the individual

defects may be detected in the fetus. Hence, prenatally diagnosed cases become more comparable to postnatally diagnosed cases and in our population the association between prenatal diagnosis and cardiac death as well as pre- and postoperative mortality disappeared. We focused on cardiac death and operative mortality as a prenatal diagnosis will have limited effect on other causes of death.

Prenatal screening for chromosomal anomalies and non-cardiovascular malformations has been enhanced during our study and these anomalies are often overrepresented in the prenatally diagnosed population<sup>2,5</sup> as the presence of these anomalies indicates a thorough cardiac evaluation. Furthermore, they have been shown to increase mortality<sup>5</sup>, thus creating further selection bias. Our findings only ascertained an association between non-cardiovascular malformations and prenatal diagnosis; however, the occurrence was not associated with increased TOP or mortality.

Additionally, fetuses with a prenatal diagnosis were born at a lower gestational age and with a lower birth weight than patients diagnosed postnatally, which may impact the prognosis and outweigh the benefit of prenatal diagnosis<sup>27,28</sup>.

Fundamentally, selection bias cannot be avoided in pre- and postnatally diagnosed groups. An ethically feasible method to overcome this, is a comparison of lesions of equal severity e.g. in TOF, where the size of the pulmonary arteries and VSD varies and impacts the outcome<sup>29</sup>. Unfortunately, the measurements necessary to identify comparable lesions within subgroups were unobtainable in our study. Fuchs *et al.* conducted a retrospective study where echocardiographies were reviewed to ensure comparability between the groups and they found improved pre-surgical status and longer catheter intervention-free survival in the prenatal group<sup>16</sup>.

To reduce selection bias, we compared the non-screening period with the screening period, and found that the introduction of general screening had a positive impact on mortality related to a prenatal diagnosis, as the association with cardiac death and operative mortality was no longer significant in this period. However, the temporal change was only significant for preoperative mortality. Nonetheless, the change indicates that, while there is still a certain amount of selection bias preventing the change from becoming significant, screening all pregnancies ensures that the cases, where detection is of greatest importance, are found, and the ones that are missed have a better prognosis.

A measurable effect on mortality cannot be expected in all lesions, as certain defects may remain balanced long enough to allow detection through routine examination. For a prenatal diagnosis to make a noteworthy difference on mortality, the CHD must be fatal if not diagnosed and treated shortly after birth, as seen in TGA and UVH. All studies that found increased mortality in prenatally diagnosed children evaluated the group as a whole. However, when addressing a subgroup of lesions some studies have been able to show increased survival with a prenatal diagnosis<sup>4,9,10,16,17</sup>. Especially prenatal diagnosis of TGA has been shown to be associated with increased survival. The rapid deterioration without intervention seen in these patients facilitates the uncovering of an effect and the well-defined nature of the condition permits only a very narrow spectrum of severity, making the two groups easily compared. Nonetheless, we were unable to show a significant difference in mortality.

#### 4.1.3.

##### *Morbidity*

There was no association between timing of diagnosis and occurrence of complications. The retrospective design renders the study vulnerable to diagnostic

inaccuracies, and especially neurocognitive deficits from delayed detection of complex lesions, such as TGA, may not be captured and therefore likely underestimate the effect of prenatal detection<sup>6</sup>. As mortality decreases, morbidity will increase, as seen in our study. Therefore, focus should be placed upon complications in future studies as they become an increasingly important endpoint. We did find that patients diagnosed prenatally had a slightly longer LOS after the introduction of general screening. The explanation may be that children without a prenatal diagnosis may not present themselves with symptoms for several days, thus not requiring admission during this time.

Finally, prenatal detection has several other benefits aside from improving prognosis. It enables thorough fetal examination, parental counselling, TOP, genetic testing, optimal perinatal management by a multidisciplinary team and allows parents to adjust to the diagnosis. When assessing benefits from prenatal diagnosis these variables should be considered.

## 4.2.

### Conclusion

Comparing prenatally diagnosed CHD with postnatally diagnosed cases is challenging as selection bias is difficult to eliminate and a randomised trial is unethical. The introduction of general prenatal screening ensures that the cases where detection is of greatest importance are found. Therefore, survival has improved and the association between prenatal diagnosis and cardiac death as well as operative mortality is no longer evident.

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**Table 1. TOP and 1-year mortality rates in live-born children in Denmark in 1996-2013**

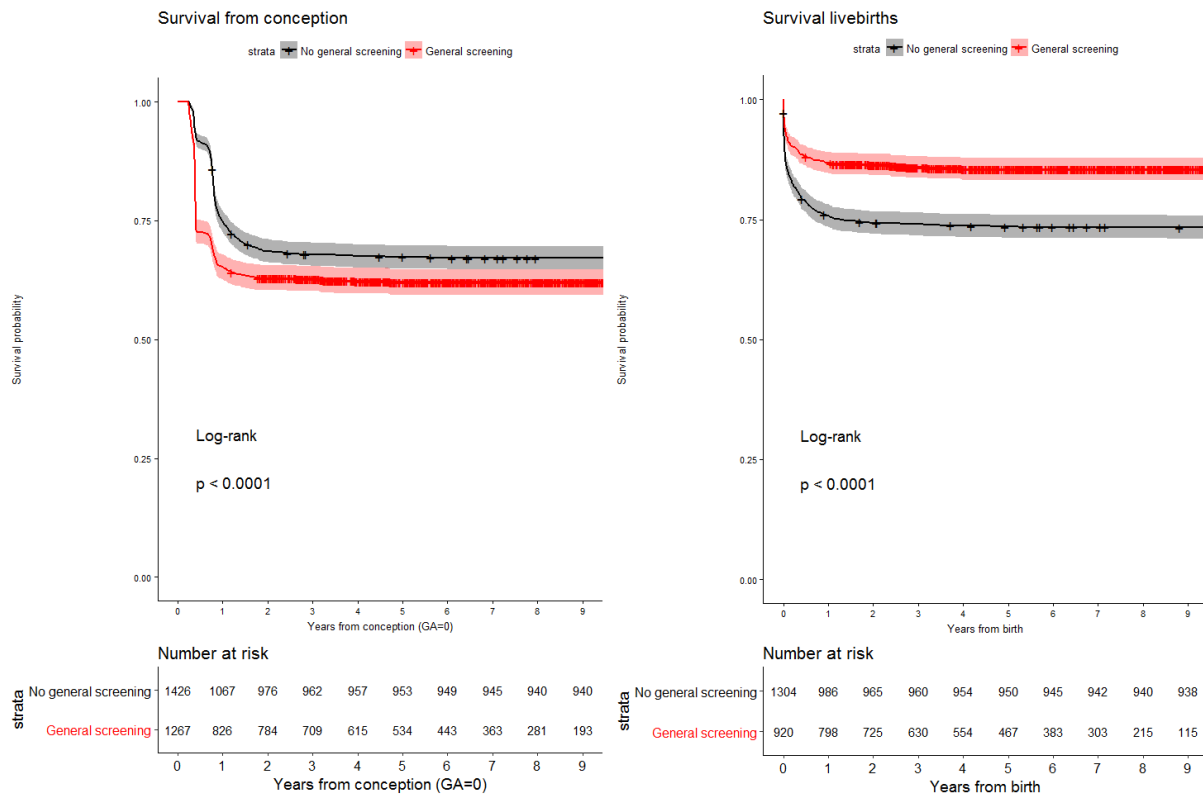
	<b>TOP</b>	<b>1-year mortality</b>	<b>TOP and 1-year mortality</b>
<b>Univentricular hearts</b>	286/638 (44.8)	185/352 (52.6)	471/638 (73.8)
<b>Congenitally corrected transposition of the great arteries</b>	6/51 (11.8)	2/45 (4.4)	8/51 (15.7)
<b>Truncus arteriosus</b>	18/61 (29.5)	21/43 (48.8)	39/61 (63.9)
<b>Transposition of the great arteries</b>	16/334 (4.8)	45/318 (14.2)	61/334 (18.3)
<b>Interrupted aortic arch</b>	6/57 (10.5)	16/51 (31.4)	22/57 (38.6)
<b>Atrioventricular septal defect</b>	93/461 (20.2)	60/368 (16.3)	153/461 (33.2)
<b>Double outlet right ventricle</b>	20/139 (14.4)	34/119 (28.6)	54/139 (38.8)
<b>Coarctation of the aorta</b>	3/490 (0.6)	21/487 (4.3)	24/490 (4.9)
<b>Ebstein's anomaly</b>	4/53 (7.5)	6/49 (12.2)	10/53 (18.9)
<b>Pulmonary atresia with ventricular septal defect</b>	5/86 (5.8)	20/81 (24.7)	25/86 (29.1)
<b>Pulmonary atresia with intact ventricular septum</b>	3/35 (8.6)	5/32 (15.6)	8/35 (22.9)
<b>Tetralogy of Fallot</b>	11/290 (3.8)	22/279 (7.9)	33/290 (11.4)
<b>Total</b>	471/2695 (17.5)	437/2224 (19.6)	908/2695 (33.7)

**Figure Legends****Figure 1.**

Survival curves before and after the introduction of general screening from conception (left) and from birth (right).

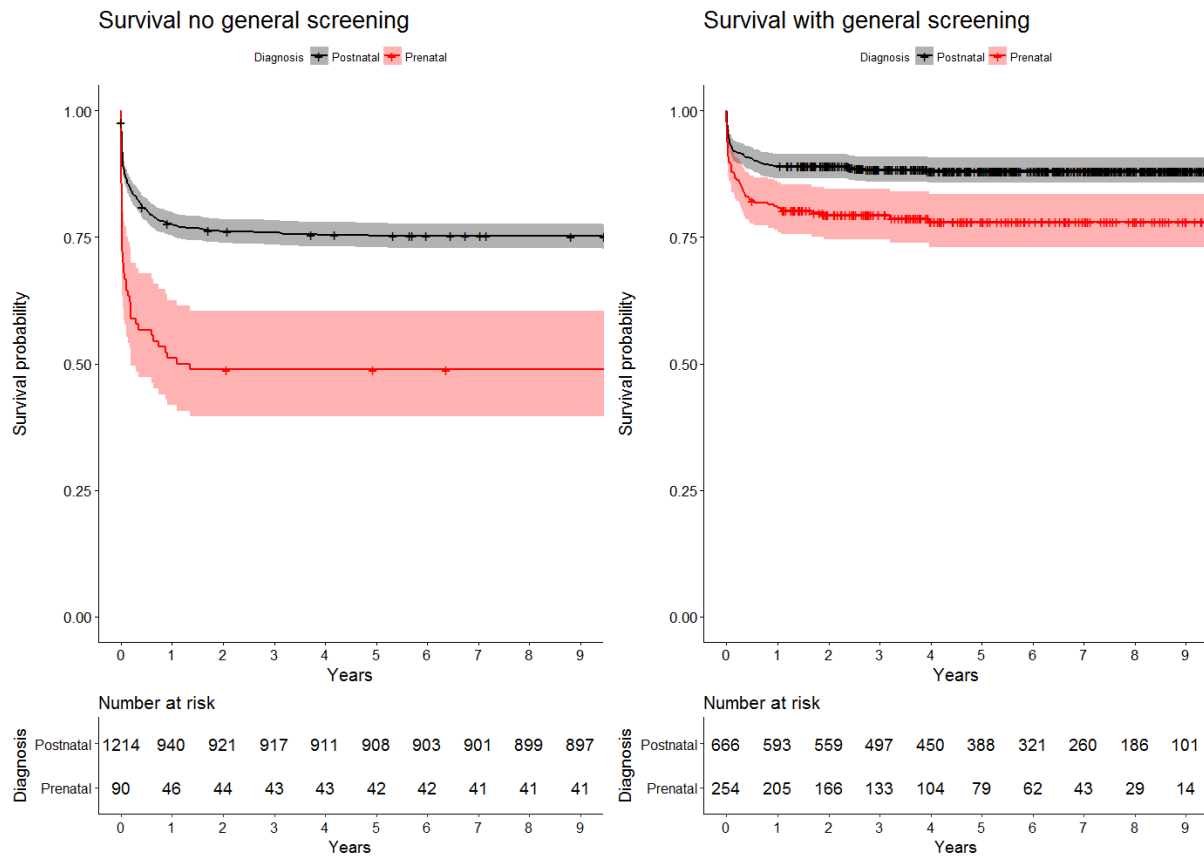
**Figure 2.**

Survival curves for prenatally and postnatally diagnosed live born children before the introduction of general prenatal screening (left) and after (right).



**Figure 1.**

Survival curves before and after the introduction of general screening from conception (left) and from birth (right).



**Figure 2.**

Survival curves for prenatally and postnatally diagnosed live born children before the introduction of general prenatal screening (left) and after (right).



**Highlights**

- Survival of major congenital heart disease is improving
- The occurrence of complications is increasing, presumably due to improved survival
- Prenatal diagnosis of major congenital heart disease is no longer associated with increased cardiac death.
- Great care must be taken when comparing prenatally diagnosed congenital heart disease with postnatally diagnosed congenital heart disease